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L3: Entry 11 of 28 File: USPT Oct 17, 2000

DOCUMENT-IDENTIFIER: US 6132980 A
TITLE: Antibodies specific for TRP-2 a human tumor antigen recognized by cytotoxic T lymphocytes

Detailed Description Paragraph Table (1):
TABLE A Cancer Therapies Based on the Molecular Identification of Cancer Antigens
1. Active immunotherapy with: a. Immunodominant peptides 1) alone 2) combined with adjuvants 3) linked to helper peptides, lipids or liposomes 4) pulsed onto antigen presenting cells b. Immunodominant peptides with amino acids substitutions to increase binding to MHC molecules c. Proteins alone or combined with adjuvants d. "Naked" DNA encoding cancer antigens 1) "gene gun" for intradermal injection 2) intramuscular injection 3) linked to lipids e. Recombinant viruses such as vaccinia, fowlpox or adenovirus encoding 1) cancer antigens alone 2) cancer antigens plus genes encoding cytokines, costimulatory molecules, or other genes to enhance the immune response f. Recombinant bacteria such as BCG, Salmonella or Listeria encoding cancer antigens alone or in combination with co-immunostimulatory molecules 2. Active immunotherapy (above) followed by the administration of co- immunostimulatory cytokines. 1. IL-2 2. IL-6 3. IL-10 4. IL-12

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L5: Entry 1 of 5 File: USPT Aug 27, 2002

DOCUMENT-IDENTIFIER: US 6440736 B1
TITLE: Altering the properties of cells or of particles with membranes derived from cells by means of lipid-modified proteinaceous molecules

Brief Summary Text (12):
In one embodiment of the invention the lipidation of the proteinaceous molecule may occur in a cell free system where the lipidation as a result of the lipidation signal is achieved by components added to the cell free system (see for instance Rusinol, A. E. J et al. Biol. Chem. 272, 8019-8025, 1997). In a preferred embodiment of the invention, the lipidation of the proteinaceous molecule is accomplished in a cell. In this preferred embodiment of the invention cellular enzymes are recruited to catalyse the lipidation of the proteinaceous molecules following a signal that is recognised by the lipidation machinery of the cell. In a particularly preferred embodiment of the invention the lipidation of the proteinaceous molecules is performed in bacteria in response to a lipidation signal recognised by the bacterial lipidation machinery. Production of a lipid-modified proteinaceous molecule in bacteria compared to eukaryotic cells generally results in higher yields. Production in bacteria is more cost effective than production in eukaryotic cells. Production of lipid-modified proteinaceous molecules in bacteria, as opposed to eukaryotic cells, for a pharmaceutical application in human and/or animal has furthermore the advantage that bacterial produced pharmaca have a significantly lower propensity for the presence of viruses and/or prions that may be harmful for a human and/or an animal. In one aspect of this particularly preferred embodiment the limidation of the proteinaceous molecules occurs in E. coli and the lipidation signal is derived from bacterial lipoprotein. In this particularly preferred embodiment the synthesis and the lipidation of said proteinaceous molecule is accomplished by introducing a recombinant DNA expression plasmid or vector into E. coli.
Glycosylphosphatidylinositol (GPI)-linked proteins form another non-limiting example of a group of proteins from of which the lipidation signal may be incorporated into a proteinaceous moiety to produce the lipid-modified proteinacecus molecules of the invention. GPI-linked proteins are plasma membrane molecules that lack a cytoplasmic tail and are attached to the plasma membrane of cells by a lipid anchor. Despite the lack of a cytoplasmic tail, GPI-linked proteins may operate as signaling molecules, conveying signals to the cell after binding of ligards or antibodies. Cell signaling via GPI-linked proteins may induce a broad variety of cellular responses, including cell activation and differentiation, apoltosis, and secretion of cytokines. Available evidence suggests that signaling via GPI-linked proteins may occur through the physical interaction of the GPI-linked protein with other membrane molecules (Simons et al., Nature 387;569-572, 1997).

Brief Summary Text (13):
In a preferred embodiment of the invention proteinaceous molecules are lipidated as a result of a lipidation signal derived from glycosylphosphatidylinositol (GPI)-linked proteins. In this preferred embodiment the lipidation of the proteinaceous molecules is achieved in eukaryotic cells, preferably yeast cells. Sequences containing the signal leading to the attachment of glycosylphosphatidylinositols moieties to proteins may be found in Udenfriend et al, Annu. Rev. Biochem. 64, 563-591 1995.

Brief Summary Text (35):
Furthermore, more than one specificity of scFv may be displayed on a single tumor cell. Thus, incorporation of an anti-CD40 LT-scFv, in addition to a targeting antibody for antigen presenting cells, may replace the requirement for T.sub.H cells

in the activation of antigen presenting cells by mimicking the CD40 ligand (Ridge, J. P. et al. 1998, Nature. 393:474-478) Ex vivo alteration of the properties of autologous tumor cells and re-infusion of the modified cells in cancer patients, or animal models of cancer, has been actively explored as a vaccination strategy for the treatment of cancer. Collectively, these approaches aim at increasing the immunogenicity of the tumor cells resulting in the induction of anti-tumor responses. Tumor cells have been genetically modified to secrete cytokines or express co-stimulatory molecules that stimulate cells of the immune system (Nawrocki, S. et al. 1999, Cancer Treat. Rev. 25:29-46). Alternatively, tumor cells have been modified by viral infection (Schirrmacher, V., et al. 1999, Gene Ther. 6:63-73), bispecific molecules (Haas, C. et al. 1999, Cancer Gene Ther. 6:254-262), haptenization of membrane molecules (Berd, D. et al. 1998, Semin. Oncol. 25: 646-653)or by fusion of tumor cells and antigen presenting cells to generate hybrids with characteristics of both the tumor and antigen presenting cell (Gong, J. et al. 1997, Nat. Med. 3:558-561). Non-modified, irradiated tumor cells have been injected into cancer patients in combination with adjuvants with considerable clinical effect (Vermorken, J. B. et al. 1999, Lancet 353:345-350). Insertion of lipid-modified proteins in the cell membrane of cancer cells builds on these findings and provides a vaccination strategy with autologous tumor cells with tailor-made properties. For example, it is within the scope of the invention to irradiated autologous tumor cells, endowed with LT-scFv specific for antigen-presenting cells and cytokines that stimulate antigen presenting cell expansion and maturation, are able to induce a vigorous anti-tumor response. Lipid-modification and expression of proteinaceous molecules in E. coli and their insertion into cell membranes is a general approach to temporarily endow a cell with single or multiple novel properties.

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L3: Entry 6 of 28 File: USPT Nov 6, 2001

DOCUMENT-IDENTIFIER: US 6312718 B1
TITLE: Vaccine for B-cell malignancies

Abstract Text (1):
A vaccine comprising a liposome preparation including at least one B-cell malignancy-associated antigen, IL-2, alone or in combination with at least one other cytokine, and at least one type of lipid molecule, is useful in a method of inducing humoral and cellular immune responses against malignant B-cells in a mammal.

Brief Summary Text (11):
Accordingly, it is an object of the present invention to provide a vaccine and method of treatment by inducing humoral and cellular immune responses against malignant B cells, in particular lymphoma, chronic lymphocytic leukemia and multiple myeloma. The vaccine comprises a liposomal preparation that incorporates at least one B cell malignancy associated antigen, at least one cytokine, and at least one type of lipid molecule. This combination therefore provides a novel and more potent vaccine formulation for B cell malignancies. The B-cell malignancy-associated antigen is preferably derived from the patient to be treated and thus the vaccine will be directed against the patient's malignant B-cells.

Brief Summary Text (12):
Thus, in one embodiment, the invention provides a vaccine comprising a liposome preparation comprising (1) at least one B-cell malignancy-associated antigen; (2) IL-2, alone or in combination with at least one other cytokine; and (3) at least one type of lipid molecule.

Brief Summary Text (17):
In another embodiment, a method for inducing humoral and cellular immune responses against malignant B-cells in a mammal is provided, comprising administering to said mammal a vaccine comprising a liposome preparation comprising (1) at least one B-cell malignancy-associated antigen; (2) IL-2, alone or in combination with at least one other cytokine; and (3) at least one type of lipid molecule.